51. (New) Mixture of claim 50, wherein the carbohydrate is selected from the group consisting of sugars, mono-, di-, tri-, oligo-, and poly-saccharides, and any physiologically acceptable derivatives, salts, forms, and solvates thereof, and any mixtures thereof.

52. (New) Mixture of claim 49, wherein the second particulate material has a median volume diameter within the range 38 to 63 μm.

53. (New) Mixture of claim 52, wherein the second particulate material has a median volume diameter within the range 45 to 63 μm.

54. (New) Composition of claim 44, wherein the first and second particulate materials are segregated upon aerosolization into a respirable first fraction and a non-respirable second fraction.

55. (New) Mixture of claim 49, wherein the first and second particulate materials are segregated upon aerosolization into a respirable first fraction and a non-respirable second fraction.

REMARKS

Status of the Claims

Upon entry of the foregoing amendments, claims 1-35 and 38-56 will be pending. Claims 1, 15, 24, 31, and 33 have been amended, claims 36 and 37 have been cancelled, and claims 38-56 have been added. No new matter has been added. In a final office action mailed March 18, 2002, claims 1-37 were rejected.

In view of the foregoing amendments and the arguments that follow, Applicants respectfully request withdrawal of all rejections upon reconsideration.

Amendments

Claim 1 has been amended to (1) delete the previously added reference to the Mohs hardness value of the second particulate material, and (2) recite that, upon aerosolization, the first and second particulate materials segregate into a respirable first fraction and a non-respirable second fraction. Support for this amendment can be found, *inter alia,* in the specification as originally filed, page 2, lines 5-9, and page 8, lines 5-12.

Claims 24 and 33 have been amended to (1) delete the previously added reference to the Mohs hardness value of the second particulate material, and (2) recite that the second particulate material be selected from the group consisting of amino acids, di-, tri-, oligo-, and poly-peptides, proteins, physiologically acceptable derivatives, forms, salts, and solvates thereof, and mixtures thereof. Support for these amendments can be found, *inter alia*, in the specification as originally filed, page 13, lines 4-15.

Claims 15 and 31 have been amended to eliminate any alleged lack of antecedent basis.

Claims 36 and 37 have been cancelled.

Claims 38 to 56 have been added. Support for these claims can be found, *inter alia*, in the specification as originally filed at page 2, lines 5-9; page 8, lines 5-12; page 13, lines 4-15; page 25, lines 3-5; and page 26, lines 1-20 and Table VI.

The Present Invention

The present invention relates to mixtures of particulate materials comprising a medicament(s) and aerosol compositions comprising these particulate materials and propellants.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 13-15 and 31-32 were previously rejected under 35 U.S.C. §112 as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Claims 15 and 31 have been amended to resolve any alleged indefiniteness. Applicants respectfully submit, however, that claim 13 complies with the requirements of §112, and amendment is not necessary. Claim 13, which recites "[c]omposition according to claim 1 wherein the propellant is selected from the group consisting of...," depends from claim 1, which recites an "[a]erosol composition comprising *a propellant*." Thus, the antecedent basis for the term 'propellant' in claim 13 is found in claim 1. *See* MPEP §2173.05(f) (claim is not improper under §112, ¶2 if it "makes reference to a preceding claim to define a limitation").

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112 of claims 13, 15, and 31, and claims 14 and 32, which depend therefrom.

Rejections Under 35 U.S.C. §102(b)

Claims 1-10 and 12-37 were rejected in the final office action ("Office Action") as allegedly being anticipated by Glaxo Group Limited (WO 96/19968, "Glaxo '968"). The examiner stated that Glaxo '968 discloses a "pharmaceutical aerosol formulation for the administration of medicaments by inhalation comprising, a particulate medicament, at least one sugar, and a fluorocarbon or hydrogen containing chlorofluorocarbon propellant." (Office Action at page 3.)

Applicants have amended claim 1 to recite that, upon aerosolization, the first and second particulate materials are segregated into a respirable first fraction and a non-respirable second fraction. Applicants respectfully submit that this claim, and claims 2-10 and 12-23 which depend therefrom, are not anticipated by Glaxo '968 because Glaxo '968 does not disclose or suggest that the second particulate material should be of a non-respirable size. In fact, Glaxo '968 teaches that smaller sizes are preferred for the second particulate material, particularly those sizes below 20 μm. (Glaxo '968 at page 4, lines 20-22.) At such smaller sizes, however, the material is respirable, and will penetrate the lungs upon inhalation. (See the specification as originally filed at page 2, lines 5-9 and page 8, lines 21-24.) In contrast, the second particulate material employed in the present invention is of a size such that it is largely non-respirable upon aerosolization. (See specification at page 8, lines 10-12.) As such, Applicants respectfully submit that claims 1-10 and 12-23 are not anticipated by Glaxo '968.

Applicants have amended claims 24 and 33 and added claim 38 to recite that the second particulate material is selected from the group consisting of amino acids, di-, tri-, oligo-, and poly-peptides, proteins, physiologically acceptable derivatives, forms, salts, and solvates thereof, and mixtures thereof. Applicants respectfully submit that these claims, claims 25-32 and 34-35 which depend therefrom, and newly added claim 38 are therefore not anticipated by Glaxo '968 as they define particulate materials that are

neither disclosed nor suggested in Glaxo. Accordingly, Applicants request that the rejections of claims 1-10 and 12-35 based on Glaxo '968 be withdrawn.

Added claims 39-54 recite narrower particle size ranges for the second particulate material, and further specify that the second particle is a carbohydrate, including sugars, mono-, di-, tri-, oligo-, and poly-saccharides, and any physiologically acceptable derivatives, salts, forms, and solvates thereof, and any mixtures thereof. Applicants respectfully submit that these new claims are also not anticipated by Glaxo '968, because Glaxo '968 does not disclose or suggest the claimed size ranges with sufficient specificity.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); MPEP §2131. Prior art which teaches a range within, overlapping, or touching the claimed range anticipates only if the prior art discloses the claimed range with sufficient specificity. MPEP §2131.03. The question of "sufficient specificity" is similar to that of whether a species can be "clearly envisaged" from a generic teaching. *See Id.*; MPEP §2131.02. Additionally, one may look to the preferred embodiments of the prior art reference to determine what can be anticipated. *In re Petering*, 301 F.2d 676 (CCPA 1962); MPEP §2131.02.

Based upon these guidelines, Glaxo '968 does not anticipate claims 39-54 of the present application, because one reading the Glaxo '968 disclosure would not be directed with sufficient specificity to use the presently claimed particle size ranges. In fact, Glaxo '968 contains only one sentence suggesting appropriate particle sizes, and states that particles with diameters smaller than 100 μm, and particularly those less than 20 μm, are preferred. (Glaxo '968 at page 4, lines 20-22.) Applicants respectfully submit that, upon reading this general statement, one of ordinary skill in the art would not clearly envisage the use of a second particulate material with the particular size range of from 38 to 200

μm, as defined in claims 39 to 54 of the present invention. Accordingly, Applicants respectfully submit that the disclosure of Glaxo '968 does not anticipate the compositions defined in new claims 39-54, and request withdrawal of all rejections based on 35 U.S.C. §102(b).

Rejections Under 35 U.S.C. §103

Claims 1-37 were rejected in the Office Action as allegedly being obvious in view of Glaxo '968 in combination with WO 95/24889 ("Glaxo '889") and WO 92/06675 ("Schultz"). Applicants respectfully traverse these rejections, and submit that newly added claims 38-56 are likewise not rendered obvious by these references.

To establish a *prima facie* case of obviousness, three basic criteria must be met.

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP §2142. As stated above, Glaxo '968 teaches only the use of sugars as the second particulate material and does not teach or suggest the claimed size ranges for those sugars or that the second particulate material is of a non-respirable size. Neither Glaxo '889 nor Schultz remedies the deficiencies of Glaxo '968.

Glaxo '889 teaches a pharmaceutical composition designed to be used in dry powder inhalers comprising medicament and at least one large lactose pellet, which is composed of microfine lactose particles. The microfine lactose particle sizes described in Glaxo '889 are much smaller than those of the present invention, namely less than 15 μm and preferably less than 5 μm. (Glaxo '889 at page 2, lines 15-25.) Glaxo '889 also does not teach or suggest the use of a propellant, as defined in the present claims. In fact, because the compositions described in Glaxo '889 are intended for use in a dry powder inhaler (which is breath-activated and does not require propellant), it is submitted respectfully that one of ordinary skill in the art would have no motivation to include a

propellant in the mixture. Analogously, applicants respectfully submit that there is also no motivation to combine the Glaxo '889 reference with Glaxo '968, and neither the previously existing nor the newly added claims in the present application are rendered obvious by Glaxo '968 in view of Glaxo '889.

Similarly, Schultz does not remedy the deficiencies of either Glaxo '968 or Glaxo '889. Schultz teaches an aerosol composition comprising a medicament, propellant, and ethanol. Schultz does not teach or suggest the use of a second particulate material of any kind, let alone any of the particulate materials described and claimed in the present application. The Schultz invention is a solution in which the medicament is dissolved in ethanol to achieve a uniform and desirable dosage. (See, e.g., Schultz at page 2.) In contrast, uniformity and consistency are achieved in the present invention due to the existence of the second particulate material. (Specification as originally filed at page 4, lines 6-10 and page 7, lines 16-25.) Thus, because a solubilizing solvent (*i.e.*, ethanol) is used in the Schultz reference, one of ordinary skill in the art would not be motivated to include first and second particulate materials, and the claims of the present application are not rendered obvious by Schultz in combination with either Glaxo '968 or Glaxo '889.

The present claims distinguish over Glaxo '968, Glaxo '889 and Schultz not only based on the components of the defined compositions, but also in the benefits and attributes which flow therefrom. In particular, applicants teach in the present application that superior suspension qualities are achieved in compositions in which particle sizes greater than 20 μm are used. (Specification as originally filed at page 26, lines 1-20.) Such superior suspension qualities are neither disclosed nor suggested in the compositions described in the cited prior art. Indeed, as noted above, Glaxo '968 teaches that the second particulate material preferably has a diameter of less than 20 μm (Glaxo '968 at page 4, lines 20-22). Accordingly, it is respectfully submitted that Glaxo '968 teaches *away* from the compositions defined in the present claims and, therefore, the advantageous properties obtained by such compositions.

For the foregoing reasons, the examiner has failed to show a *prima facie* case of obviousness based upon Glaxo '968 in view of Glaxo '889 and Schultz. Accordingly, Applicants respectfully request withdrawal of all rejections based on 35 U.S.C. §103.

Newly Added Claims 55-56

Claims 55-56 have been added to recite compositions or mixtures in which the first and second particulate materials are segregated upon aerosolization into a respirable first fraction and a non-respirable second fraction. Applicants respectfully submit that the invention as recited in these claims can be distinguished from the cited references, particularly Glaxo '968, for the same reasons discussed above with respect to claim 1. Glaxo '968 teaches that smaller particle sizes are preferred for the second particulate material, and indicates that particle sizes below 20 μm are particularly preferred. (Glaxo '968 at page 4, lines 20-22.) At such smaller sizes, the particulate material will penetrate into the lungs when the aerosol is inhaled. (Specification as originally filed at page 2, lines 5-9, and page 8, lines 21-24.) In contrast, the present invention employs a second particulate material that separates upon aerosolization and is non-respirable in size. Because this distinction is nowhere recognized or described by Glaxo '968, Applicants respectfully submit that newly added claims 55-56 are not anticipated by or rendered obvious in view of Glaxo '968, and therefore define patentable subject matter over the cited prior art.

Conclusion

Applicants believe that the pending claims have been adequately distinguished from the prior art previously cited by the examiner. Accordingly, a Notice of Allowance for all of pending claims 1-35 and 38-56 is respectfully requested. The examiner is invited to telephone the applicants' undersigned representative at (215) 557-5966 if he wishes to discuss the application further.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned, "**Version With Markings to Show Changes Made**.".

Respectfully submitted,

Date: January 21, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 1 has been amended as follows:

1. (Twice amended) Aerosol composition comprising a propellant and contained therein a first particulate material comprising particles having a median aerodynamic diameter within the range 0.05 μm to 11 μm and a second particulate material comprising particles having a median volume diameter within the range 15 to 200 μm, wherein the first and second particulate materials are segregated upon aerosolization into a respirable first fraction and a non-respirable second fraction [wherein the second particulate material has a Mohs hardness value of less than 6.5].

Claim 15 has been amended as follows:

15. (Amended) Composition according to claim 14 wherein the propellant is a hydrofluoroalkane selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and mixtures thereof.

Claim 24 has been amended as follows:

24. (Twice amended) Pharmaceutical composition comprising a propellant and contained therein a particulate medicament comprising particles having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material comprising particles having a median volume diameter within the range 15 to 200 μm, wherein the second particulate material is selected from the group consisting of amino acids, di-, tri-, oligo-, and poly-peptides, proteins, physiologically acceptable derivatives, forms, salts, and solvates thereof, and mixtures thereof [wherein the second particulate material has a Mohs hardness value of less than 6.5].

Claim 31 has been amended as follows:

31. (Amended) A method for preparing a [an aerosol] composition according to any one of claims 1 to 24 comprising admixing the ingredients together prior to dispensing into a container and sealing the container.

Claim 33 has been amended as follows:

33. (Twice amended) A mixture of first particulate material having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material having a median volume diameter within the range of 15 to 200 μm, wherein the second particulate material is selected from the group consisting of amino acids, di-, tri-, oligo-, and poly-peptides, proteins, physiologically acceptable derivatives, forms, salts, and

solvates thereof, and mixtures thereof [wherein the second particulate material has a Mohs hardness value of less than 6.5].

The following claims have been added:

38. (New) Composition of claim 1 wherein the second particulate material is selected from the group consisting of amino acids, di-, tri-, oligo-, and poly-peptides, proteins, physiologically acceptable derivatives, forms, salts, and solvates thereof, and mixtures thereof.

39. (New) Aerosol composition comprising a propellant and contained therein a first particulate material comprising particles having a median aerodynamic diameter within the range 0.05 μm to 11 μm and a second particulate material comprising particles having a median volume diameter within the range 38 to 200 μm.

40. (New) Composition of claim 39, wherein the second particulate material is a carbohydrate.

41. (New) Composition of claim 40, wherein the carbohydrate is selected from the group consisting of sugars, mono-, di-, tri-, oligo-, and poly-saccharides, and any physiologically acceptable derivatives, salts, forms, and solvates thereof, and any mixtures thereof.

42. (New) Composition of claim 39, wherein the second particulate material has a median volume diameter within the range 38 to 63 μm.

43. (New) Composition of claim 42, wherein the second particulate material has a median volume diameter within the range 45 to 63 μm.

44. (New) Pharmaceutical composition comprising a propellant and contained therein a particulate medicament comprising particles having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material comprising particles having a median volume diameter within the range 38 to 200 μm.

45. (New) Composition of claim 44, wherein the second particulate material is a carbohydrate.

46. (New) Composition of claim 45, wherein the carbohydrate is selected from the group consisting of sugars, mono-, di-, tri-, oligo-, and poly-saccharides, and any physiologically acceptable derivatives, salts, forms, and solvates thereof, and any mixtures thereof.

47. (New) Composition of claim 44, wherein the second particulate material has a median volume diameter within the range 38 to 63 μm.

48. (New) Composition of claim 47, wherein the second particulate material has a median volume diameter within the range 45 to 63 μm.

49. (New) A mixture of first particulate material having a median aerodynamic diameter within the range 0.05 to 11 μm and a second particulate material having a median volume diameter within the range of 38 to 200 μm.

50. (New) Mixture of claim 49, wherein the second particulate material is a carbohydrate.

51. (New) Mixture of claim 50, wherein the carbohydrate is selected from the group consisting of sugars, mono-, di-, tri-, oligo-, and poly-saccharides, and any physiologically acceptable derivatives, salts, forms, and solvates thereof, and any mixtures thereof.

53. (New) Mixture of claim 49, wherein the second particulate material has a median volume diameter within the range 38 to 63 μm.

54. (New) Mixture of claim 53, wherein the second particulate material has a median volume diameter within the range 45 to 63 μm.

55. (New) Composition of claim 44, wherein the first and second particulate materials are segregated upon aerosolization into a respirable first fraction and a non-respirable second fraction.

56. (New) Mixture of claim 49, wherein the first and second particulate materials are segregated upon aerosolization into a respirable first fraction and a non-respirable second fraction.